Cognitive and Attentional Function in Pediatric Hypoplastic Left Heart Syndrome

By

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CHAPTER 1

GENERAL INTRODUCTION

The number of youths living with chronic illness is increasing due to advances in condition detection and treatment (Halfon & Newacheck, 2010). In particular, the prevalence of congenital heart disease (CHD) has dramatically increased in children and adults in recent years, particularly more severe forms of CHD (Marelli, Ionescu-Ittu, Mackie, Guo, Dendukuri, & Kaouache, 2014). It is estimated that approximately 1,000,000 children and adolescents are living with CHD (Compas, Jaser, Reeslund, Patel, & Yarboi, 2017). While increased survival is the ultimate goal for these children, concerns are raised regarding increased reliance on health care systems, decreased quality of life, increased parental caretaking, and abnormal brain development (Compas et al., 2017; Miller et al. 2007). Increased prevalence intersects with potentially challenging outcomes for these youth.

Hypoplastic left heart syndrome (HLHS) is a severe congenital heart defect characterized by impairment in the development of the left side of the heart, including the mitral valve, aortic valve, and aorta. Consequently, infants with HLHS are unable to pump oxygen-rich blood through the body. Standard of care primarily includes a series of palliative surgical interventions beginning in the newborn period and extending through early childhood (Norwood procedure, bidirectional Glenn procedure, followed by the Fontan procedure) to increase blood flow and bypass the underdeveloped left side of the heart, allowing the right ventricle to become the main pumping chamber to the body (Feinstein et al., 2012). Prior to the advent of modern surgical techniques, HLHS was universally fatal.

While CHD is the most common congenital disorder, HLHS is arguably the most severe form of CHD (Canfield et al., 2006). The estimated prevalence of HLHS is only a fraction of

other CHDs (Benjamin et al., 2018), yet there is evidence that these children show the largest deficits in multiple domains of cognitive function (Karsdorp, Everaerd, Kindt, & Mulder, 2007). Deficits in cognitive function can affect educational and occupational attainment, earning potential, as well as psychosocial and behavioral development via disease- and treatment-related mechanisms (Compas et al., 2017).

There is a need to document the magnitude, pervasiveness, and specificity of cognitive and attentional difficulties in children with HLHS. The present thesis addresses this by updating and extending the current literature on children and adolescents with HLHS with a systematic review and meta-analysis on cognitive function in this population (Chapter 2). In addition, the detailed cognitive profiles and level of attention problems in a sample of youth with HLHS are presented (Chapter 3), and findings discussed.

CHAPTER 2

COGNITIVE FUNCTION IN PEDIATRIC HYPOPLASTIC LEFT HEART SYNDROME: SYSTEMATIC REVIEW AND META-ANALYSIS

2.1 Introduction

After the advent and adoption of palliative surgical procedures for HLHS, life expectancy for these children has significantly increased with 10-year survival reaching 89% (d'Udekem et al., 2014), leading to increased attention on survivors. Despite improvements in procedural techniques for HLHS repair, children continue to have compromised postoperative systemic cardiac output, reduced systemic oxygen delivery, high systemic oxygen extraction, and anaerobic end-organ dysfunction (Feinstein et al., 2012). Children with HLHS have more surgeries, cardiac catheterizations, and hospitalizations compared to children with other complex congenital heart lesions and have been identified as being at the highest risk for developmental disability (Gerstle, Beebe, Drotar, Cassedy, & Marino, 2016; Marino et al., 2012). Reductions in social competence, communication, and adaptive behavior have also been noted (Ikle, Hale, Fashaw, Boucek, & Rosenberg, 2003). As the number of children surviving with HLHS has increased, tracking their long-term function has become increasingly important.

One of the primary long-term consequences of HLHS is impaired cognitive development and brain function. HLHS and other types of CHD are associated with increased risk for neurodevelopmental disabilities (Mahle & Wernovsky, 2001; Marelli, Miller, Marino, Jefferson, & Newburger, 2016). Two meta-analytic reviews have summarized findings on cognitive deficits in children with HLHS from infancy through 12 years of age. First, in a meta-analysis of cognitive function in children and adolescents with several types of CHD, Karsdorp and colleagues analyzed four studies reporting Full Scale IQ (FSIQ), Verbal IQ (VIQ), and

Performance IQ (PIQ) published up to 2005 (Karsdorp, et al., 2007). Results showed large deficits in FSIQ and PIQ, and medium deficits in VIQ for children with HLHS. Children with other forms of CHD showed negligible to small deficits in FSIQ, VIQ, and PIQ. This finding implies that the long-term cognitive effects of HLHS may be greater than those of other forms of CHD. Sistino and Bonilha (2012) reported secondary analyses of IQ as a part of a larger quantitative review reporting changes in hospital survival in preschool and school-aged children with HLHS using 10 studies published up to 2010. Preschool children with HLHS scored in the low average range on the Bayley II Mental Development Index. They also examined FSIQ, assessed by standardized measures of intelligence in school-aged children (ages six to 12 years), and the mean FSIQ of children with HLHS was in the low average range.

Findings reported by Karsdorp et al. (2007) and Sistino and Bonilha (2012) highlight the importance of further investigation of cognitive function for children with HLHS and provide a baseline for the field; however, these reviews had several limitations. First, Karsdorp et al. (2007) only included four studies of children with HLHS available at that time, with a mean sample age ranging from 2.8 to 9.0 years. Sistino and Bonilha reported mean FSIQ across studies for school-aged children, but not standardized effect sizes for functioning in both pre-school and school-aged children. Finally, neither of the previous reviews assessed moderators of effect sizes. Due to evidence of the cumulative and synergistic nature of risk factors associated with CHD throughout development (Marelli et al., 2016), child age may be related to increased deficits in functioning. Children with CHD are living through adolescence and early adulthood (d'Udekem et al., 2014); the inclusion of adolescents is imperative to understanding the long-term impact of HLHS on cognition. Further, as medical protocols and interventions improve over time, study publication year may also be an important moderator of effects.

A quantitative review of the current research on cognitive function in children with HLHS can help to identify gaps in the literature and establish directions for future research, practice, and intervention. The goal of the present meta-analysis is to provide an updated quantitative review of all literature reporting cognitive function in children with HLHS, utilizing standardized tests of broad indices of cognitive function, including FSIQ, VIQ, and PIQ in order to replicate and extend findings from previous meta-analyses. The aims were to (1) determine levels of FSIQ, VIQ, and PIQ relative to the normative mean in children and adolescents with HLHS; and (2) determine if child age and study publication year act as linear moderators of these deficits.

2.2 Methods

Literature Search and Inclusion Criteria

I searched for original empirical studies to identify articles that examined cognitive functioning in children and adolescents with HLHS up to February 1st, 2019 with no lower bound date in order to maximize available data. The systematic literature search was conducted using PubMed and PsycINFO, with three specific sets of search terms. The first was (*cognition OR cognitive function OR intelligence) AND (hypoplastic left heart syndrome OR HLHS)* across all fields (i.e., title, abstract, keywords); the second was (*neurocognitive OR cognitive function OR cognitive impairment OR intellectual impairment OR cognitive deficit OR executive function) AND (hypoplastic left heart syndrome OR HLHS)*; and the third was *(neurodevelopmental OR neuropsychological) AND (hypoplastic left heart syndrome OR HLHS)*. PubMed and PsycINFO searches were supplemented using backward searches reviewing the reference sections of published meta-analyses including HLHS and cognitive function. Studies were included if they contained original empirical data on cognitive function reporting (a) standardized Wechsler measures of intelligence (e.g., WPPSI or WISC or WASI); (b) data on children between 2 years

and 6 months and 17 years of age; (c) data for a sample of children with HLHS.

Data Coding

The following information was extracted from each study where available: (a) measures of cognitive function; (b) sample size; (c) sample mean age; (d) publication year; and (e) summary statistics for the calculation of effect sizes. All studies were independently coded by two raters and discrepancies were resolved through discussion. Inter-rater reliability was .98. Cognitive function scores were categorized into (a) FSIQ, (b) VIQ, and (c) PIQ. One study (Oberhuber et al., 2017) reported more specific Wechsler scale composite scores. In this case the Verbal Comprehension Index and Working Memory Index were coded into VIQ, and the Perceptual Reasoning Index and Processing Speed Index were coded into PIQ. Each index score was entered into the Comprehensive Meta-Analysis program (Version 3; Borenstein, Hedges, Higgins, & Rothstein, 2013), and data was collapsed within the program by using mean of the selected outcome and study as the unit of analysis. For studies providing only the median and confidence intervals for the data, the mean and standard deviation were calculated (Hozo et al., 2005). Cohen's (1988) guidelines for effect size interpretation were used.

Study Quality

Criteria from the National Institutes of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (NHLBI, 2014) were adapted for the current review, excluding items that were irrelevant to or inconsistent with the study aims and inclusion/exclusion criteria. Studies were assigned one point per each criterion met, which were summed for a total quality score of 0 – 7 (0 indicating lowest quality and 7 highest quality).

Statistical Approach

All analyses were conducted with the Comprehensive Meta-Analysis program (Version 3;

Borenstein et al., 2013), using random effects models, as the studies varied in methodology and design; study as the unit of analysis; mean of the selected outcome measure for effect sizes; and subgroup within study as the unit of analysis for age analyses in order to capture all studies reporting any HLHS subgroups. For each cognitive domain, standardized weighted mean effect sizes (g), which correct for biases associated with small sample sizes, 95% confidence intervals, and an estimated heterogeneity statistic (Q) were calculated using the procedure of Hedges and Olkin (1985). The 95% confidence intervals of the weighted mean effect sizes represent the range in which the mean effect size will be in 95% of cases. Mean effects are considered significant if the confidence interval does not include zero. Simple meta-regression analyses using mixed effects models were conducted to analyze effects of continuous moderator variables.

Publication Bias

Systematic bias can lead to inflated estimates of effect sizes and incorrect conclusions as a result of selective publication for result direction or size. To assess for possible publication bias, funnel plots were examined, Egger's tests were calculated to detect funnel plot asymmetry, and trim and fill analyses were performed indicating how many studies would need to be included to achieve funnel plot symmetry (Egger et al., 1997; Duval & Tweedie, 2000).

2.3 Results

Study Characteristics

A total of 118 studies were screened for eligibility. Seventy-three studies did not report Wechsler measures of cognitive function, one reported one individual Wechsler subtest, and 11 did not report outcomes specific to an HLHS group (see Figure 1 for a PRISMA diagram). Thirteen studies met the specified inclusion criteria ($N = 358$). The mean age across studies was 6.95 years. Thirteen reported FSIQ and ten reported VIQ and PIQ. Descriptive statistics of each

study and individual effect sizes can be found in Table 1.

Effect Sizes

Scores on measures of cognitive function in samples of children and adolescents with HLHS were significantly lower than the normative mean across all domains (Table 2). Findings showed large deficits in FSIQ, g = -.87, 95% CI [-1.10, -.65]. The mean FSIQ was 86.88 across studies and ranged from 70.40 to 94.90 (Figure 2). There was a medium effect for deficits in VIQ, g = -.61, 95% CI [-.96, -.50], with an overall mean of 90.82 across studies, ranging from 81.32 to 98.90 (Figure 3). The largest deficit was seen in PIQ, g = -.89, 95% CI [-1.11, -.68]. The mean PIQ across studies was 86.56, ranging from 78.00 to 94.50 (Figure 4). All models had significant heterogeneity, indicating the presence of potential moderators (Table 2).

Moderator Analyses

Meta-regression analyses of Hedges' g on child age revealed a significant effect for FSIQ, coefficient = -.07, 95% CI [-.12, -.01], $p < .05$, $R^2 = .40$, indicating that every year of increased age corresponds to a loss of 1.1 FSIQ points (Table 3; Figure 5). There were no significant methodological moderators of FSIQ; total number of subtests in the FSIQ measure (p = .27), number of working memory subtests (p = .32), and number of processing speed subtests (p = .24) were all non-significant. Child age was not associated with VIQ (p = .39) or PIQ (p = .16). No significant effects were found in regression analyses of Hedges' g for study publication year: FSIQ (p = .15), VIQ (p = .29), or PIQ (p = .13).

Quality Assessment

Quality ratings are depicted in Table 1 and Figure 6. Seven criteria were used and study quality ranged from 4 to 7 (M = 5.46, SD = .21). Overall, studies infrequently included sample size justification/power analyses and rarely reported whether outcome assessors were blinded to

participant status/diagnosis. Study quality ratings were not related to effect sizes for FSIQ (r = -.29; p = .34), VIQ (r = .11, p = .76), or PIQ (r = -.17, p = .65).

Publication Bias

The effect size for FSIQ revealed a non-significant Egger's test (regression intercept = -2.91 95% CI [-6.40, 0.57]), VIQ was non-significant (regression intercept = -0.91, 95% CI [-6.35, 4.52]), and PIQ was also non-significant (regression intercept = 0.13, 95% CI [-5.00, 5.26]). The funnel plots for the effect sizes are presented in Figure 7. Trim and fill analyses revealed that the effect size for FSIQ required three values to be added to create a symmetrical funnel plot. Notably, this result remained significant, and these adjusted values are presented in Table 2. Taken together, there is no evidence for publication bias.

2.4 Discussion

The present meta-analysis of cognitive function in children and adolescents with HLHS builds on previous research by providing an update of the literature, including both children and adolescents, examining multiple domains of cognitive function (FSIQ, VIQ, PIQ), and assessing the moderating effect of age on cognition. Findings replicated and extended previous research in children with HLHS, showing medium to large deficits relative to the normative mean across cognitive domains, and significant heterogeneity in all models, indicating potential moderators. A novel finding revealed that child age was a significant linear moderator of FSIQ across studies, such that greater sample mean age was associated with larger deficits in mean scores.

The results showed large deficits in FSIQ and PIQ, and medium deficits in VIQ. The relatively larger deficits for PIQ compared to VIQ may be understood within the framework of fluid and crystallized intelligence (Fry & Hale, 2000). Fluid intelligence, most closely aligned with PIQ, is not static, can be affected by many maturational and experiential processes, and has

been shown to be affected by intra- and perioperative factors in children with single ventricle defects, while crystalized intelligence was not (Vahsen, Bröder, Hraska, & Schneider, 2018). The pattern of effect sizes reported here include 13 studies of cognitive function in youth with HLHS and expand on findings from a previous meta-analysis of four studies from a decade prior (Karsdorp et al., 2007). This consistent pattern, in conjunction with non-significant effects for publication year in meta-regressions, indicates that these effects may be stable and highlights the potential need for additional assessment and services for children and adolescents with HLHS.

Significant heterogeneity in the effects found in the current meta-analysis could reflect the presence of moderators. There was significant heterogeneity in effects for VIQ, a composite of verbal comprehension and working memory, and PIQ, a composite of perceptual reasoning and processing speed, which may reflect variability among more specific cognitive functions. Previous research has been limited in that most studies have only examined overarching domains of cognitive function, while more specific domains are underutilized. Researchers are calling for complete evaluations on all domains of cognitive functioning in CHD as deficits in certain domains may support the presence of pathological substrates secondary to cardiac defects or surgery (Compas, et al., 2017). Once a sufficient number of studies are available, assessing more specific domains of verbal comprehension, working memory, perceptual reasoning, and processing speed will be important in future research in order to delineate profiles of deficits for targeted interventions.

Only one study to date reports more specific domains of cognitive function, with a sample of 43 children with HLHS. Oberhuber and colleagues (2017) report overall FSIQ in the low average range (M = 84.5, SD = 20.8), with scores ranging from 40 to 134. FSIQ was positively skewed, where more children scored in the below average range. There was a distinct pattern of

individual index scores, with variability between verbal comprehension, perceptual reasoning, processing speed, and working memory. In addition to FSIQ, verbal comprehension (M = 84.0, SD = 23.2), perceptual reasoning (M = 83.6, SD = 18.0), and processing speed (M = 84.5, SD = 18.0) means were all in the low average range and positively skewed, with a larger proportion of children scoring in the lower ranges. Of note, working memory scores were in the average range (M = 101.8, SD = 18.8) and normally distributed. Alternatively, in a study of children aged 10 to 19 years with single ventricle lesions requiring the Fontan procedure (40% HLHS), children scored significantly lower on working memory (M = 92.7, SD = 15.8) than a referent group and the population mean (Bellinger et al., 2015). Future research should continue to utilize measures of specific domains of cognitive function in order to determine areas needing additional support.

Although emerging evidence suggests that children with all forms of CHD may be at risk for long-term neuropsychological consequences as they grow into adolescence and young adulthood (Marino et al., 2012), this is the first meta-analysis to show that age is significantly related to child FSIQ in HLHS. Specifically, each year of increased mean sample age reflected a loss of 1.1 IQ points across studies, highlighting the importance of early intervention for children with HLHS, as cognitive deficits appear to be greater in older HLHS samples. It is important to note that this finding is limited as it is based on linear moderator analyses across studies, rather than within a cross-sectional sample or a longitudinal design.

There are three potential explanations for this finding. First, cognitive decline with age may reflect ongoing brain injury in children with HLHS, who are at high risk for stroke and with chronic hypoxia (Marelli et al., 2016; Watson, Stopp, Wypij, Newburger, & Rivkin, 2017). Second, without presuming further injury, cognitive function may worsen over time due to compromised integrative function during development. As cognitive and educational demands

become more complex and abstract, children with HLHS may not be able to keep up with peers and make expected gains. Third, lower IQ among older children may be a result of cross-sectional study designs. For example, older child age may reflect older surgical and perfusion practices, resulting in potentially greater impact on cognition. In support of this idea, one study found that overall IQ in children with HLHS increased with year of surgery from 1989 to 1999 (Sistino & Bonilha, 2012). However, in the present analyses, year of surgery and operative information were not available, therefore we are unable to determine if younger children benefitted from improved techniques. Taken together, there is need for longitudinal studies, as well as research accounting for differences in treatment procedures within samples.

Marelli and colleagues (2016) argue that the opportunity for neurological injury and risk factors for negative developmental outcomes may be synergistic over time, with the brain at increased risk for vulnerability to injury. For those with CHD, the cumulative burden of reduced cardiovascular function in childhood and adolescence may lead to progressive cerebrovascular disease with age. Furthermore, children post-Fontan aged 10 to 19 years have been shown to have reduced brain volumes and cortical thickness compared to controls (Watson et al., 2017). The authors hypothesized that there may be greater regional reduction in gray matter volume among youth with Fontans due to hypoxia and relatively reduced cerebral perfusion characteristic of HLHS. In addition, white matter maturation is important for the development of cognitive functions (Nagy, Westerberg, & Klingberg, 2004). As compared to those without white matter injury, school-aged children with CHD and white matter injury have been shown to have lower FSIQ scores (Claessens et al., 2018). Similar results have been found in pediatric conditions, where decreased white matter maturation corresponded to lower cognitive function scores (e.g., premature birth, cancer survivorship) (Bells et al., 2018; Keunen et al., 2017). Other

clinical populations have demonstrated a similar effect of decreased cognitive function in older children. For example, increased age has been shown to correspond to decreased FSIQ in children with sickle cell disease (Compas et al., 2017; King et al., 2014). Because both CHD and sickle cell disease are present from birth, child age also reflects illness duration. Therefore, accounting for age is important in the interpretation of these results, as cognitive deficits could reflect actual decreases in abilities or the failure to progress at the same rate as healthy peers.

With regards to heterogeneity due to other potential moderators, studies of children with single ventricle defects and Fontan procedure survivors report FSIQ scores ranging from low average to average, with some correlating with various factors including preoperative cerebral tissue oxygen saturation, birth weight, head circumference, age at surgery, postoperative length of stay, and seizure history (Gaynor et al., 2014; Goldberg et al., 2000; Hansen et al., 2016; Ikle et al., 2003; Kern, Hinton, Nereo, Hayes, & Gersony, 1998; Mahle et al., 2000; Mahle et al., 2006; Oberhuber et al., 2017; Sarajuuri et al., 2012; Watson et al., 2017). It will be important for future research to explore correlates and potential factors contributing to variability in cognitive domains to better understand the effects of the disease and its treatment.

In light of research showing that working memory is affected by CHD (Bellinger et al., 2003), as well as risk of white matter injury affecting processing speed in this population, I analyzed the total number of subtests, and number of working memory and processing speed subtests as potential moderators. Since older children may be administered larger test batteries, they may appear to be performing worse than their younger counterparts as a function of the subtests included in analyses. None of the possible moderator effects were significant, suggesting that these findings were not due to the number of subtests included.

Studies of children with HLHS often do not account for comorbidities that may contribute to

cognitive deficits. While some researchers note that results with exclusionary criteria are not generalizable to high-risk patients with HLHS, cognitive functioning cannot be attributed solely to an HLHS diagnosis (Mahle et al., 2006). In a sample of young children with HLHS, 25 percent had a genetic syndrome or abnormality, and these children were found to have lower mental development scores (Newburger et al., 2012). Future research should examine how these factors affect cognitive function in children with HLHS.

While the search strategy was limited to HLHS in an attempt to focus on a more homogeneous study population rather than including all children with single ventricle physiology who had undergone a Fontan procedure, it is important to note that children with other single ventricle lesions may have similar risks for cognitive deficits (Bellinger et al., 2015). Research also indicates that children with single ventricle defects, including HLHS, have higher rates of grade retention, more missed school days, and lower school competency, in addition to more surgeries, catheterizations, and fewer years since last hospitalization compared to those with two-ventricle lesions (Gerstle et al., 2016). In light of academic issues and barriers to academic engagement, following these children and adolescents into adulthood will be of utmost importance as cumulative disease burden may affect employment and quality of life. While research on adults with HLHS in particular is limited, adults with CHD report a higher prevalence of cognitive, physical, and activity limitations and decreased cognitive function compared to norms (Farr, Oster, Simeone, Gilboa, & Honein, 2016; Tyagi et al., 2014). The widespread and lifelong implications of HLHS call for interdisciplinary efforts involving physicians and psychologists to improve outcomes via closely monitoring risk for neurodevelopmental issues and employing early interventions to mitigate potential cognitive deficits for this population (Rappaport, 2015).

While contributing important findings to the literature, the present study highlights limitations that should be addressed in future empirical research. Research on HLHS across development has been sparse and includes small samples, therefore only 13 studies met inclusion criteria, all of which were cross-sectional ($N = 358$). The average age of all samples included in the present analyses was approximately seven years old, and in light of age effects, the field would benefit from assessing cognitive function across development and into adulthood. In addition, I was only able to assess broad domains of cognitive function. Future research should employ full cognitive batteries, reporting more specific indices of cognitive function, since overall FSIQ may not reveal accurate cognitive profiles of youth with HLHS, nor be a true indicator of all skills. Study quality should also be considered when interpreting results from this systematic review. Quality assessment analyses highlighted limitations in the included studies. For example, only two studies specified whether assessors were blinded to participants' status/diagnosis or study objectives. And while most studies noted sample size as a limitation, few conducted a priori power analyses or reported effect sizes. This further underscores the need for meta-analyses to better understand cognitive functioning in HLHS survivors.

Future research should seek to determine factors contributing to more specific domains of cognitive function, including preoperative, operative, and postoperative factors, and other potential moderators. Intervention research would benefit this population by finding evidence-based methods for improving cognitive function. Finally, studies in CHD and other pediatric populations have shown that deficits in cognitive function are related to lower use of adaptive coping skills and increased internalizing symptoms (Prussien et al., 2018; Jackson, Gerardo, Monti, Schofield, & Vannatta, 2018). A previous meta-analysis found that in addition to cognitive deficits, children with CHD are at risk for psychosocial problems, including

internalizing and externalizing behavior problems, especially in older children and adolescents (Karsdorp et al., 2007). This highlights the importance of delineating cognitive and psychosocial impairments in children with HLHS in order to provide adequate services and support.

Due to advances in surgical and medical care, survival for children with HLHS has increased dramatically, yet this population has been shown to have increased risk for cognitive deficits and lower quality of life compared to other chronic illnesses and complex congenital heart lesions (Gerstle et al., 2016; Marelli et al., 2016; Marino et al., 2012; Sistino & Bonilha, 2012). The present meta-analysis confirms and updates the current literature for FSIQ, VIQ, and PIQ and expands the review of cognitive function in children with HLHS to a wider age range. In addition, measures of FSIQ, VIQ, and PIQ in children with HLHS were lower than norms, with medium and large effects, and have significant heterogeneity. Furthermore, increased child age predicted larger effects for deficits in FSIQ. These findings highlight the importance of further longitudinal research following children with HLHS through development tracking cognitive outcomes, and the need for early intervention to improve cognitive function and quality of life in this population.

CHAPTER 3

COGNITIVE AND ATTENTION PROFILES IN CHILDREN WITH HYPOPLASTIC LEFT HEART SYNDROME

3.1 Introduction

As 90% of children with HLHS now survive past infancy due to advances in surgical techniques and post-operative intensive care unit management, the importance of following these children into their school age years and beyond is amplified. In spite of the significant advances in treatments, questions remain regarding long-term cognitive and behavioral functioning in this high-risk population (Feinstein et al., 2012). In a meta-analysis of cognitive function in children and adolescents with HLHS, Siciliano et al. (in press) reported on 13 studies of cognitive function in children with HLHS and found significant deficits in Full Scale IQ (FSIQ), Performance IQ (PIQ), and Verbal IQ (VIQ). In addition, Siciliano et al. found that larger deficits in FSIQ were associated with child age, where each year of increased mean sample age corresponded to a loss of 1.1 IQ points. This finding highlights the possibility that children with HLHS may experience ongoing brain injury with age or decreased cognitive function associated with the increasing cognitive demands with age, as older children with HLHS perform more poorly than healthy peers (e.g., Marelli, Miller, Marino, Jefferson, & Newburger, 2016; Watson, Stopp, Wypij, Newburger, & Rivkin, 2017). However, the majority of these studies sampled young children and less is known about older school-aged children who may experience increased cognitive, academic, and behavioral demands and expectations.

In addition, much prior research has focused on broad cognitive function in children with HLHS, and few studies have reported more specific indices of cognitive function beyond FSIQ, VIQ, and PIQ (i.e., verbal comprehension, visual spatial ability, fluid reasoning, working

memory, and processing speed). One exception can be found in a recent study reporting all indices of the Wechsler Intelligence Scales for Children, Fourth Edition (WISC-IV) in 43 children aged 6.3 to 16.9 with HLHS (Oberhuber, et al., 2017). In this sample, FSIQ was in the low average range (M = 84.5), ranging from 40 to 134, and positively skewed. Verbal comprehension (M = 84.0), perceptual reasoning (M = 83.6), and processing speed (M = 84.5) were also in the low average range and positively skewed. Notably, working memory was the only index in the average range (M = 101.8) and normally distributed. However, in other heterogenous samples of adolescents and adults with CHD, significant deficits have been found in working memory on the WISC-IV (Bellinger et al., 2015; Murphy et al., 2017). A reliable cognitive screening tool would be useful in this high-risk population to determine children who may benefit from more comprehensive cognitive testing.

In addition to mounting evidence of cognitive deficits, children with CHD, including HLHS, are at greater risk for attention problems. A meta-analysis indicated that children with CHD perform more poorly on measures of attentional function (Sterken, Lemiere, Vanhorebeek, Van den Berghe, & Mesotten, 2015), and several studies have found that inattention is the most commonly reported problem in children specifically with HLHS and single ventricle defects (e.g., Brosig, Mussatto, Kuhn, & Tweddell, 2007; Gaynor et al., 2014; Mahle et al., 2000). When compared to healthy, unaffected sibling controls, adolescents and young adults with other complex lesions show elevated rates of attention problems (Murphy et al. 2017). Furthermore, within CHD subtypes (tetralogy of Fallot, transposition of the great arteries, and those with single ventricle anatomy requiring the Fontan palliation, including HLHS), children post-Fontan had increased parent reports of inhibition problems compared to controls, and were statistically more likely to have parent-reported problems with initiation and working memory compared to

children with transposition of the great arteries (Cassidy, White, DeMaso, Newburger, & Bellinger, 2015). In adolescents, DeMaso et al. (2017) found that those with single ventricle physiology were more likely to have lifetime or current psychiatric disorder compared to controls, particularly anxiety disorders and attention deficit hyperactive disorder (ADHD), and scored more poorly than controls on measures of global psychosocial functioning.

Children with single ventricle defects, particularly those who have undergone the Fontan palliation, are at high risk for adverse medical outcomes, decreased birth weight, and extended postoperative length of stay (LOS; e.g., Baker-Smith, Goldberg, & Rosenthal, 2015; Desai et al., 2017; Gaynor et al., 2014; Kalfa et al., 2015; Pizarro, Davies, Woodford, & Radtke, 2015; Tabbutt et al., 2012). While low birth weight (LBW) and greater LOS have been associated with poorer medical outcomes in HLHS, fewer studies have investigated their relationship to cognitive and attentional function, and most focus on children very early in development showing correlations between birth weight and LOS with cognitive development (Knirsch et al., 2012; Mahle et al., 2013; Naef et al., 2017; Newburger et al., 2012). Longer LOS has corresponded to lower VIQ, PIQ, and FSIQ in school-aged children (Mahle et al. 2006). Therefore, medical or disease factors that may contribute to variability in cognitive and attentional function deserve greater attention.

In light of the relatively small number of studies reporting specific indices of cognitive function, and evidence of attentional problems, the current study focused specifically on these domains in a group of children and adolescents with HLHS. A battery of both cognitive and behavioral measures was completed to determine levels of impairment in the sample. I hypothesized that children with HLHS would (1) demonstrate below average scores on cognitive measures compared to norms and (2) have increased attention problems compared to norms. I

also expected that effects would be large for attention problems and all cognitive measures, poorer cognitive function would be related to more attention problems, and that risk factors for poorer medical outcome (i.e., LBW and prolonged LOS) would be correlated with cognitive deficits and attention problems.

3.2 Methods

Participants

Participants included 20 school-aged children with HLHS (M = 11.20, SD = 2.55), 75% were male, 90% were White non-Hispanic and 10% were Hispanic. Children and adolescents were recruited from pediatric cardiology clinics at a large children's hospital in the southern United States. Inclusion criteria were (a) diagnosis of HLHS and completion of the Fontan palliation and (b) 8 to 16 years of age. Exclusion criteria were (a) DiGeorge Syndrome (chromosome 22q11 deletion), Down Syndrome, or other suspected genetic syndromes, (b) known neurological impairment, (c) prematurity with gestational age <37 weeks, or (d) epilepsy.

All participants had an initial surgery during infancy. The median age at first cardiac surgery was four days (interquartile range = 2.25 to 6.75 days). On average, participants had three cardiac surgeries prior to age five (range = 3 to 5). Additional surgeries beyond the standard three surgeries for HLHS were to address post-operative complications such as mediastinal fluid drainage, clot removal, or pacemaker placement. Participant characteristics are reported in Table 4. At the time of the study, 20% of participants were on medication for ADHD, 30% had repeated a grade in school at the time of assessment, 45% had received special education services at some point, and 10% reported receiving special classroom accommodations (e.g., extra time, adjusted assignment and exam length).

Measures

Cognitive function. The Wechsler Intelligence Scale for Children – Fifth Edition (WISC-V; Wechsler, 2014), a widely used and well-validated measure of cognitive function and intelligence, was administered to all participants. For the current analyses, FSIQ and the five indices, Verbal Comprehension (VCI), Visual Spatial (VSI), Fluid Reasoning (FRI), Working Memory (WMI) and Processing Speed (PSI), were examined. Participants also completed the National Institutes of Health Toolbox Cognition Battery (NTBC; Gershon et al., 2013), which yields a Fluid Cognition Composite. The NTBC is a standardized, computerized battery intended to serve as a brief (30 min) and convenient battery of neuropsychological function for children.

Child attention problems. Parents reported their child's school, social, and psychological functioning on the Child Behavior Checklist (CBCL) and children filled out the Youth Self Report (YSR; Achenbach & Rescorla, 2001). The Attention Problems subscales were used from both. Scores are presented as normalized *T*-scores ($M = 50$, $SD = 10$) based on age and sex. Reliability and validity are well established for these measures (Achenbach & Rescorla, 2001).

Risk factors for cognitive deficits. Seven applicable risk factors for developmental disability were rated as present (1) or not present (0) from medical charts (Marino et al., 2012). Risk factors included: (1) developmental delay recognized in infancy, (2) history of mechanical circulatory support (extracorporeal membrane oxygenation or ventricular assist device use), (3) heart transplant, (4) cardiopulmonary resuscitation at any point, (5) prolonged hospitalized (postoperative LOS > 2 weeks in hospital), (6) perioperative seizures related to CHD surgery, and (7) significant abnormalities on neuroimaging or microcephaly. These were summed to create a linear overall risk factor score. Risk factor characteristics for the full sample are reported in Table 5. Postoperative LOS for first surgery was the only significantly skewed variable. Two participants had LOS scores greater than two standard deviations from the mean. When

categorized as outliers and excluded from analysis, the data were no longer skewed (M = 41.70, SD = 23.92).

Procedure

The study was approved by the Institutional Review Board, and informed consent and assent were obtained from parents and children, respectively. A pediatric neurologist conducted a standard neurology exam on all children and adolescents. During a separate laboratory-based study visit, children and parents completed questionnaires. Children then completed a cognitive assessment administered by graduate and postdoctoral-level research assistants. Participants were reimbursed for their time at the conclusion of the study visit.

Statistical Power and Data Analyses

Statistical analyses were conducted with SPSS (version 25). Means, standard deviations, and one-sample *t*-tests were computed to test hypotheses. All *t*-tests were two-tailed. Bivariate correlations (Pearson's *r*) were also calculated to assess the association between scores of cognitive function, questionnaire measures of attention problems, birth weight, LOS, and cumulative risk. Exploratory correlations between the NTBC and WISC-V indices were included to determine the potential clinical utility of this brief measure as a screening tool in clinical settings. Power analyses indicated that with n = 20, α = .05, and power of .80, significant differences of medium-to-large effect sizes could be detected for norm difference t tests (d > .66) and correlations (r > .55). Cohen's (1988) guidelines to interpret effect sizes were used.

3.3 Results

Cognitive Function

Scores of cognitive function relative to the normative mean are described in Table 6. Performance on FSIQ, VCI, VSI, and PSI assessed by the WISC-V were significantly lower than

the normative mean, showing large effects (FSIQ d = 1.08; VCI d = 1.33; VSI d = .80; PSI d = 1.00) (Table 6). Similarly, participants scored significantly lower than the normative mean on the NTBC Fluid Cognition Composite with a large effect (d = .79). Scores on the WISC-V FRI and WMI were in the average range and were not statistically different from the standardization sample, p = .12 and p = .06, respectively.

On five out of seven measures of cognitive function, 50% or more of the sample scored in the below average classification range (i.e., scores lower than 90). Sixty percent of children in the sample scored below average on the overall FSIQ, along with 65% of participants on the VCI, 50% on the VSI, 60% on the PSI, and 65% on the NTBC Fluid Cognition Composite (Table 7). In contrast, 40% scored below average on the FRI, and 25% scored below average on the WMI.

Attention Problems

Self and parent-reported attention problems are also described in Table 6. Youth self-report on the YSR revealed significantly elevated difficulties in attention compared to standardized norms (d = .81), and parent report on the CBCL also reflected significantly elevated scores on the Attention Problems scale (d = 1.01); both effects were large. Five percent of parents rated their children as having clinically significant attention problems (greater than the 98th percentile), and 11% of parents rated their children has having borderline clinical attention problems (greater than the 94th percentile). In contrast, 11% of children rated themselves at the clinical level and 22% rated themselves above the borderline clinical level for attention problems.

Exploratory Correlational Analyses

Child age was negatively correlated with VSI, r = -.52, p = .02, where older participants had lower visual spatial ability scores. There were two participants defined as outliers for postoperative LOS for first surgery. With these two scores removed, postoperative LOS for first

surgery was positively related to CBCL attention problems, $r = .54$, $p = .02$, where longer stays corresponded to increased parent-reported attentional problems. With all participants included, this was no longer significant. The number of cardiac risk factors was negatively associated with self-reported attention problems, $r = .55$, $p = .02$, where participants with more cardiac risk factors had decreased reports of attentional problems. Birth weight was not significantly related to any measures of cognitive function or attention problems. No measures of cognitive function were significantly related to self- or parent-reported attention problems. Exploratory correlations showed the NTBC Fluid Cognition Composite was significantly related to the WISC-V VCI ($r = .45$, $p = .05$), FRI ($r = .46$, $p = .04$), WMI ($r = .78$, $p < .001$), PSI ($r = .48$, $p = .03$), and FSIQ ($r = .57$, $p = .008$), with only WMI and FSIQ remaining significant after correcting for multiple comparisons.

3.4 Discussion

The present study provides detailed assessment of cognitive and attentional function in children with HLHS, and is one of only a few studies on cognition in school-aged children and adolescents with HLHS. The results reflect significantly lower scores on most cognitive measures compared to the normative mean, and effects ranged from medium to large. Large effects were observed for indices measuring verbal comprehension, visual spatial abilities, and processing speed, and overall FSIQ. WMI scores approached significance, and FRI were non-significant, and both were in the average range. While the sample of children with HLHS scored lower than the normative mean in multiple cognitive domains, there are important differences in the overall profile of more specific indices of cognitive function, which highlights opportunities for targeted intervention in these children.

While meta-analyses of cognitive function demonstrate that children with HLHS score below their same-age peers on global cognitive measures, including FSIQ, VIQ, and PIQ (Karsdorp, Everaerd, Kindt, & Mulder, 2007; Siciliano et al., in press), only one other study to date reports more specific domains of cognitive function in the HLHS population (Oberhuber et al., 2017). Similar to the present findings, the overall FSIQ was in the low average range in their sample of children with HLHS. There was also a distinct pattern of individual index scores on the WISC-IV. Specifically, measures of verbal comprehension (M = 84.0), perceptual reasoning (M = 83.6), and processing speed (M = 84.5) were all in the low average range, while working memory was in the average range (M = 101.8). In another study of children and adolescents with single ventricle lesions requiring the Fontan procedure (40% HLHS), Bellinger et al. (2015) found that children scored significantly lower on working memory tasks (M = 92.7). While scores on the WMI in the current sample did not differ significantly from the norms, the mean (M = 93.7) closely resembles that found by Bellinger and colleagues.

It is noteworthy that the Perceptual Reasoning Index score was split into visual spatial and fluid reasoning abilities when moving from the WISC-IV, used by Oberhuber and colleagues, to the WISC-V, used in the current study. The results with the WISC-V show that VSI was significantly lower than the normative mean, while FRI was not. This highlights the importance of utilizing specific measures of cognitive function. These differences may be illustrative in developing specific and targeted interventions for impaired domains of cognitive function while also acknowledging relative strengths.

In five out of seven measures of cognitive function, half or more of the sample scored in the "below average" range (Table 7). While this is not synonymous with school performance, it may indicate a need for additional supports moving into academic spheres. In the current sample, 30%

of children had repeated a grade in school, 45% received special education services, and 10% reported special classroom accommodations. Another study has shown that the majority of families of very young children with HLHS are not accessing early interventions (Mussatto et al., 2018). Similar to children with other chronic health conditions, thorough cognitive testing may be an avenue in which children with HLHS can receive the most helpful and fitting classroom modifications to optimize outcomes (Compas et al., 2017).

While visual spatial ability was related to child age, the current results showed no other relationships between cognitive scores and child age. VSI scores were negatively related to child age, where older child age corresponded to poorer visual spatial scores. While numerous studies have reported deficits in visual spatial and visual motor skills in children with HLHS (Gaynor et al., 2014; Brosig et al., 2013; Sarajuuri et al., 2007), others have not (Brosig et al., 2007), and none reported differences in these abilities with age. Further, while limited, research in adults with CHD has shown high percentages scoring below norms on measures of cognitive and attentional function, particularly those with single ventricle defects (Tyagi, Austin, Stygall, Deanfield, Cullen, & Newman, 2014; Tyagi et al., 2017). Therefore, age effects should be prioritized for research in larger, longitudinal samples.

Exploratory correlational analyses revealed that postoperative LOS was not significantly related to any cognitive scores in this sample. In HLHS, postoperative LOS has been related to medical factors (Mosca et al., 2000), malnutrition (Kelleher, Laussen, Teixeira-Pinto, & Duggan, 2006), and/or lack of typical environmental inputs (e.g., school, communication) (Sananes et al., 2012). Other medical and operative factors, including age at first surgery, increased number of anesthetic exposures, and operative complications, have been associated with lower cortical volume and thickness in post-Fontan children (Diaz et al., 2016; Watson et al., 2017), and

children with biventricular cardiac lesions show decreased brain volumes compared to controls, which corresponded to language development (Rollins et al., 2017). Furthermore, in school-aged children, longer LOS after first cardiac surgery corresponded to decreased VIQ (Mahle et al. 2006). Investigation of these factors in larger samples should be pursued in future research.

In terms of attention problems, both parent- and child-reported problems on the CBCL and YSR were significantly elevated compared to normative samples with large effects. This is consistent with previous research showing that children with single ventricle lesions are more likely to meet criteria for ADHD (DeMaso et al., 2017). In general, children with CHD demonstrate more attention problems as measured by parent- and teacher-rated reports of attention compared to other heart lesions (Brosig et al., 2007), as well as compared to normative samples (Brosig et al., 2013; Shillingford et al., 2008) and healthy sibling controls (Murphy et al., 2017). This demonstrates that this population may benefit from a focus on attention in intervention.

Correlational analyses between attentional problems and medical risk factors yielded disparate results. Neither child self-reported nor parent-reported attention problems were related to child age or birth weight. Of note, this may reflect evaluation bias, as children born premature were excluded (< 37 weeks), which may have restricted the range for correlations with LBW, and those with lowest birth weights may be less likely to survive into middle childhood. However, LOS was positively related to parent-reported attention problems, consistent with hypotheses. This relationship indicates that children with HLHS may benefit from an increased emphasis on cognitive and behavioral interventions in order to bolster against the negative sequelae of disease, surgery, and perioperative-related consequences. Yet further research is necessary in order to determine relationships with perioperative risk factors, as other reports of

inattention and hyperactivity in children with complex cardiac lesions have shown no significant correlations between pre-, intra-, or postoperative variables (Shillingford et al., 2008). Contrary to hypotheses, the cardiac risk factor score was negatively related to self-reported attention problems in children. This finding appears to be anomalous, where more risk factors corresponded to lower scores on children's self-reported attention problems in this sample.

The inclusion of the NTBC, a standardized, computerized battery may be of particular interest to medical providers, as it is intended to serve as a brief and efficient battery to assess of neuropsychological function in children (Weintraub et al., 2013). It may be an easy tool to administer in any hospital or outpatient faculty by staff to get an adequate screen of cognitive function to identify children who may have cognitive impairments. These analyses indicate that the Fluid Cognition Composite is significantly correlated with VCI, FRI, WMI, PSI, and FSIQ, and correlations ranged from medium to large in magnitude. Since youth with HLHS appear to demonstrate poorer cognitive outcomes compared to other CHD subtypes, a brief cognitive screening tool such as this one would be helpful in identifying those who may require further testing to determine particular strengths or areas in need of more support for optimal achievement.

While the current study adds to the literature, findings are also limited by small sample sizes and a fairly homogeneous sample. Indeed, this is a general problem for the field, as most studies examining cognitive function in HLHS include small samples that are underpowered to detect smaller effects (Siciliano et al., in press). It will be important to study these factors in larger, multi-center samples of youth with HLHS, since there appears to be variability in children with HLHS in the previous literature and the present results. Future research should also investigate potential demographic correlates, as there is evidence that parental education also contributes to

performance in children with HLHS (Oberhuber et al., 2017). In addition, while the focus was only on children with HLHS in an attempt to delineate cognitive and attentional profiles in a homogeneous sample, it is important to note that children with other single ventricle lesions are also at risk for cognitive impairment (Bellinger et al., 2015).

In summary, the current study reported a comprehensive assessment of cognitive functioning, including the WISC-V and NTBC battery, as well as reports of attentional problems in a sample of school-aged children and adolescents with HLHS. Specific domains of cognition, beyond the overarching measures of FSIQ, VIQ, and PIQ, have been understudied in this population: Only one study to date has reported more specific indices of cognitive function (Oberhuber et al., 2017). The present study extends these findings with an updated assessment of cognitive function and the NTBC battery. This sample demonstrated large deficits in FSIQ, VCI, VSI, PSI, and attention problems compared to norms, all of which could considerably affect school and employment outcomes. While many children are scoring in the below average range across many domains of cognitive function, there is nonetheless a subset of this population that is scoring in the average or above average ranges. Future research should ascertain factors contributing to cognitive performance to pinpoint specific potential areas of dysfunction in order to adequately provide targeted services and support for children with HLHS and their families.

CHAPTER 4

GENERAL DISCUSSION

The results from the present meta-analysis and cross-sectional study move the field forward in terms of understanding the magnitude of deficits in cognitive function in children with HLHS, specific profiles of cognitive domain function, levels of attention problems, and potential disease-related correlates in these youth. Taken together, these results provide important data evidencing significant cognitive deficits both across studies and within a sample of children with HLHS, highlighting the need for increased monitoring in this population for those working with these families in clinical practice. Children with HLHS seem to be particularly at risk for cognitive deficits compared to children with other forms of CHD and their healthy peers according to the literature and the present results (Karsdorp et al., 2007; Marelli et al., 2016). Therefore, early cognitive testing is warranted, as well as the need for tracking long-term outcomes via continued assessment across development.

In sum, the present studies support the need for a more sensitive and developmentally focused system of care for children with chronic illness, particularly HLHS (Halfon & Newacheck, 2010). Future research should investigate potential tools to identify children at highest risk for adverse cognitive and behavioral outcomes, as well as seek to identify potential modifiable targets for intervention (e.g., medical risk factors). Specifically, screening measures, cognitive remediation programs, and attentional training may be beneficial for youth with HLHS in order to adequately assess, and potentially mitigate, negative outcomes.

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Table 1

Mean Standard Scores for IQ Testing and Differences Between Groups

Study	Year	Country	Study Design	n	Mean Age (years)	Female (%)	Race (% white)	Seizure Hx (%)	Cognitive Measure	IQ-HLHS	Difference	Effect Size (*g*)	Study Quality
Creighton et al.	2007	CA	C	14	5.00	31	80	--	FSIQ	85.00	-15.00	-1.00	5
									VIQ	--	--	--	
									PIQ	--	--	--	
Gardner	2004	US	C	31	6.35	41	--	7	FSIQ	79.42	-20.58	-1.36	6
									VIQ	81.32	-18.68	-1.24	
									PIQ	81.23	-18.77	-1.24	
Gaynor et al.	2010	US	C	67	4.00	40	73	--	FSIQ	94.90	-5.10	-.34	5
									VIQ	--	--	--	
									PIQ	--	--	--	
Goldberg et al.	2000	US	C	26	4.00	33	--	10	FSIQ	93.80	-6.20	-.41	6
									VIQ	98.90	-1.10	-.07	
									PIQ	89.70	-10.30	-.68	
Hansen et al.	2016	DE	C	42	4.50	35	--	--	FSIQ	94.00	-6.00	-.40	5
									VIQ	97.00	-3.00	-.20	
									PIQ	93.00	-7.00	-.47	
Ikle et al.	2003	US	C	13	5.20	19	--	--	FSIQ	88.54	-11.46	-.76	5
									VIQ	90.54	-9.46	-.63	
									PIQ	88.85	-11.15	-.74	
Kern et al.	1998	US	C	12	4.40	43	--	14	FSIQ	80.67	-19.33	-1.29	5
									VIQ	86.83	-13.17	-.88	
									PIQ	78.00	-22.00	-1.47	
Mahle et al.	2000	US	C	28	8.90	37	--	--	FSIQ	84.50	-15.50	-1.03	5
									VIQ	87.50	-12.50	-.83	
									PIQ	82.25	-17.75	-1.18	
Mahle et al.	2006	US	C	47	12.50	32	88	23*	FSIQ	85.50	-14.50	-.97	4
									VIQ	88.50	-11.50	-.77	
									PIQ	84.50	-15.50	-1.03	
Oberhuber et al.	2017	AT	C	43	10.30	35	--	5	FSIQ	84.50	-15.50	-1.02	6
									VIQ	92.90	-7.10	-.47	
									PIQ	84.05	-15.95	-1.06	
Sarajuuri et al.	2007	FI	C	7	5.98	--	--	--	FSIQ	86.70	-13.30	-.89	4

									VIQ	89.90	-10.10	-.67	
									PIQ	89.60	-10.40	-.69	
Sarajuuri et al.	2012	FI	C	23	5.15	--	--	26	FSIQ	90.25	-9.75	-.65	5
									VIQ	92.75	-7.25	-.48	
									PIQ	94.50	-5.50	-.37	
Wernovsky et al.	2000	US	C	5	14.10	45	--	7*	FSIQ	71.00	-29.00	-1.93	6
									VIQ	--	--	--	
									PIQ	--	--	--	
Overall				**358**	**6.95**								

Note. AT = Austria; CA = Canada; DE = Germany; FI = Finland; US = United States of America; C = cross-sectional; FSIQ = Full Scale IQ; VIQ = Verbal IQ; PIQ = Performance IQ. Mean Age = the mean sample age. Seizure Hx = seizure history. Difference is calculated from the normed IQ (M = 100). Study Quality = total study quality rating ranging from 0 to 7. -- = study did not report this measure. * = denotes that the seizure history value was for preoperative seizure history, whereas all others were postoperatively assessed.

Table 2

HLHS Meta-Analysis on Neurocognitive Deficits

Level	*k*	g	95% CI	Q
Full Scale IQ	13	-.87***	-1.10 to -0.65	48.56***
Adjusted value		-.73***	-.96 to -.50	73.27***
Verbal IQ	10	-.61***	-0.84 to -0.38	30.11***
Performance IQ	10	-.89***	-1.11 to -.68	26.27**

Note. *k* = number of studies included; g = mean effect size (Hedges' *g*); Q = estimated heterogeneity statistic. Adjusted values are shown for any effect size in which trim and fill analyses indicated publication bias.
*p < .05; **p < .01; ***p < .001

Table 3
Meta Regression Analyses of Hedges' g on Child Age

Covariate	Coefficient	Std Error	95% CI	Z	Total R^2
FSIQ					.40
Intercept	-.38	.23	-.83 to .07	-1.65	
Child Age	-.07	.03	-.12 to - .01	-2.30*	
VIQ					.00
Intercept	-.37	.31	-.99 to .24	-1.19	
Child Age	-.03	.04	-.11 to .04	-0.85	
PIQ					.23
Intercept	-.56	.26	-1.07 to -.05	-2.16*	
Child Age	-.05	.03	-.02 to .02	-1.42	

Note. FSIQ = Full Scale IQ; VIQ = Verbal IQ; PIQ = Performance IQ.
* $p < .05$, ** $p < .01$, *** $p < .001$

Table 4
Participant Demographic and Medical Characteristics

	Mean	SD	Range
Age	11.20	2.55	8 - 16
Gender (% male)	75	--	--
Age at first cardiac surgery (days)	5.10	3.67	1.97 - 16.02
Cardiac surgeries before age 5	3.40	.60	3 - 5
First surgery postoperative LOS (days)	77.51	85.30	12 - 328
Birth weight (kg)	3.30	.56	2.24 – 4.36
Cardiac risk factors	2.10	1.17	0 - 4

Note. LOS = length of stay; Cardiac risk factors = total number of cardiac risk factors per subject (open heart surgery in first year of life, other cyanotic heart lesions not requiring open heart surgery, any combination of congenital heart disease, developmental disability recognized in infancy, history of mechanical circulatory support (extracorporeal membrane oxygenation or ventricular assist device), heart transplant, cardiopulmonary resuscitation, prolonged hospitalization, perioperative seizures related to heart surgery, significant neuroimaging abnormalities or microencephaly). $N = 20$.

Table 5
Cardiac risk factors

	No. Cases	Percentage
Comorbidities	18	90
Developmental delay	9	45
Hx of mechanical support	6	30
Heart transplant	1	5
Cardiopulmonary resuscitation	4	20
Prolonged hospitalization (> 2 wks)	17	85
Perioperative seizures	3	15
Significant neuroimaging abnormality*	2	10

Note. Hx = history; wks = weeks; *Neuroimaging abnormalities included acute infarct and restricted diffusion. *N*=20.

Table 6
Cognitive and Attentional Functioning

	Total Sample		Norm Comparison	
	Mean	SD	*t*	*d*
WISC-V				
VCI	84.40	11.71	-5.96***	1.33
VSI	88.55	14.24	-3.60**	.80
FRI	94.80	14.39	-1.62	.36
WMI	93.65	13.89	-2.05^{+}	.46
PSI	87.90	12.12	-4.46***	1.00
FSIQ	85.45	13.44	-4.84***	1.08
NTBC Composite	85.65	18.20	-3.53**	.79
YSR Attention Problems	58.11	9.53	3.61**	.85
CBCL Attention Problems	60.11	7.62	5.78***	1.33

Note. Cognitive outcomes and comparing to normative samples including effect sizes. WISC-V = Wechsler Intelligence Scale for Children; VCI = Verbal Comprehension Index; VSI = Visual Spatial Index; FRI = Fluid Reasoning Index; WMI = Working Memory Index; PSI = Processing Speed Index; FSIQ = Full Scale IQ; NTCB Composite = NIH Toolbox Cognitive Battery Fluid Cognition Composite; YSR = Youth Self Report; CBCL = Child Behavior Checklist. WISC-V indices and NTBC composite scores are compared to standard scores: *M* = 100; YSR and CBCL scores are compared to T scores: *M* = 50. N=20 for WISC-V and NTCB scores, N=18 for the YSR scores. N=19 for the CBCL scores.
$^{+}$ p < .06, * p < .05, ** p < .01, *** p < .001

Table 7
Numbers and percentages of children in each standardized classification

	Below Average (< 90) n (%)
WISC-V	
VCI	13 (65)
VSI	10 (50)
FRI	8 (40)
WMI	5 (25)
PSI	12 (60)
FSIQ	12 (60)
NTBC Composite	13 (65)

Note. Below Average = standard scores less than 90; WISC-V = Wechsler Intelligence Scale for Children – Fifth Edition; VCI = Verbal Comprehension Index; VSI = Visual Spatial Index; FRI = Fluid Reasoning Index; WMI = Working Memory Index; PSI = Processing Speed Index; FSIQ = Full Scale IQ; NTBC Composite = NIH Toolbox Cognitive Battery Fluid Cognition Composite.

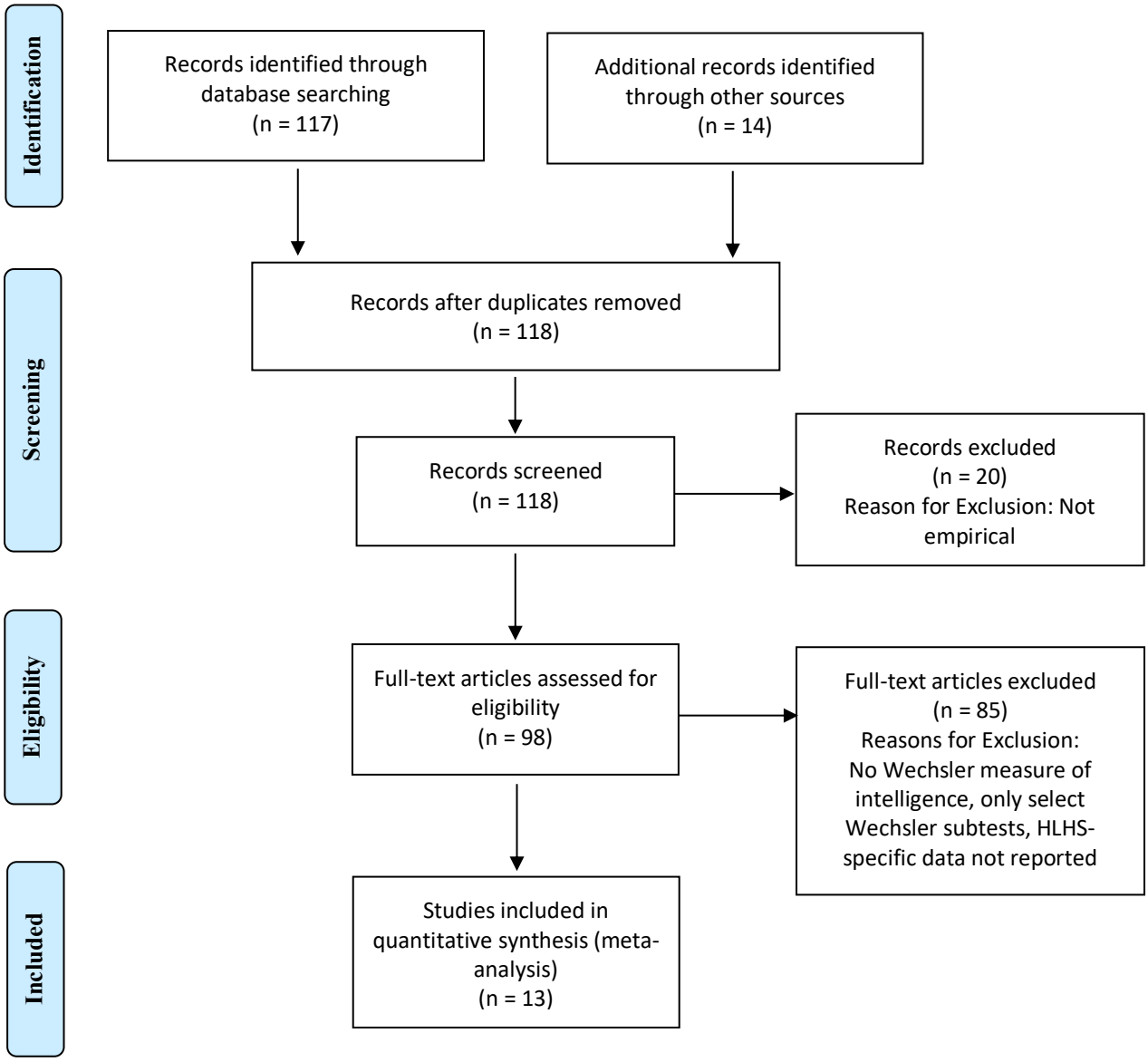

Figure 1. PRISMA flow diagram.

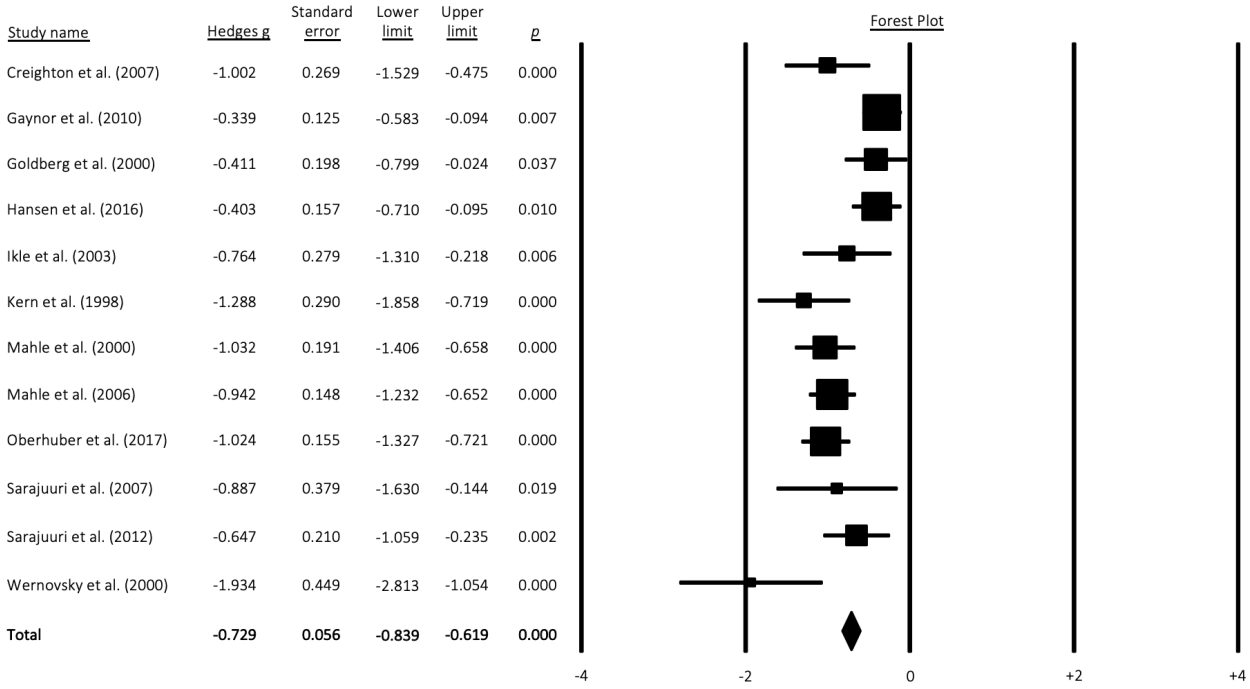

Figure 2. Forest plot depicting results for Full Scale IQ in children with HLHS relative to the normative mean. Hedges' *g* = estimate of effect size. Lower and Upper limits reflect the 95% confidence intervals for the Hedges' *g* statistic.

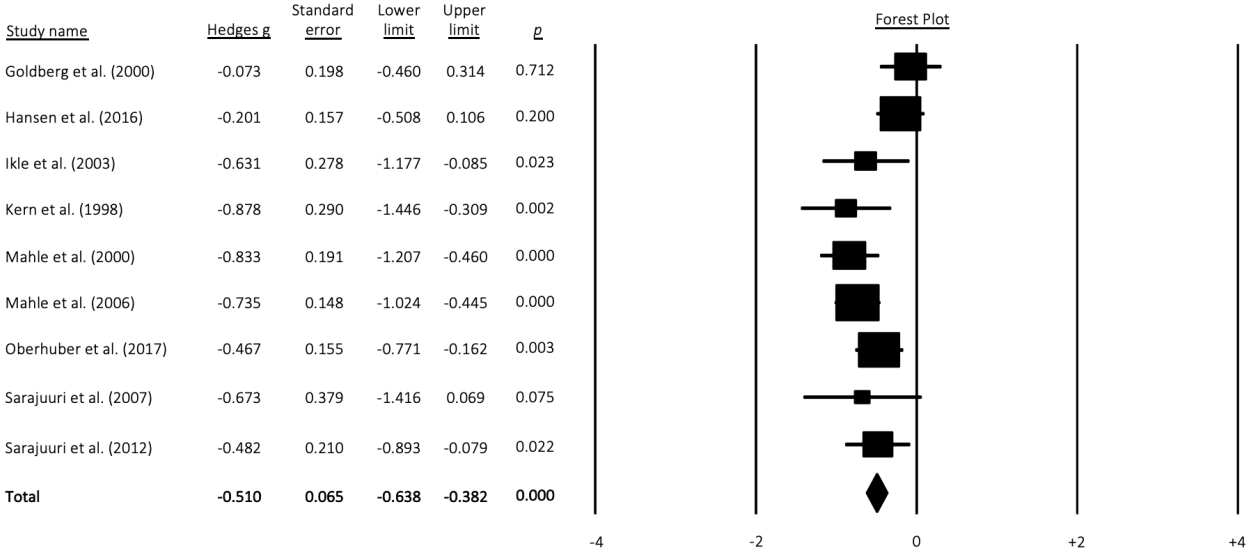

Figure 3. Forest plot depicting results for Verbal IQ in children with HLHS relative to the normative mean. Hedges' *g* = estimate of effect size. Lower and Upper limits reflect the 95% confidence intervals for the Hedges' *g* statistic.

Study name	Hedges g	Standard error	Lower limit	Upper limit	p
Goldberg et al. (2000)	-0.685	0.198	-1.073	-0.297	0.001
Hansen et al. (2016)	-0.471	0.157	-0.779	-0.163	0.002
Ikle et al. (2003)	-0.743	0.279	-1.289	-0.197	0.008
Kern et al. (1998)	-1.466	0.291	-2.036	-0.897	0.000
Mahle et al. (2000)	-1.180	0.191	-1.554	-0.806	0.000
Mahle et al. (2006)	-1.013	0.148	-1.304	-0.723	0.000
Oberhuber et al. (2017)	-1.059	0.156	-1.364	-0.754	0.000
Sarajuuri et al. (2007)	-0.693	0.379	-1.436	0.049	0.069
Sarajuuri et al. (2012)	-0.367	0.210	-0.778	-0.045	0.081
Total	**-0.847**	**0.065**	**-0.975**	**-0.719**	**0.000**

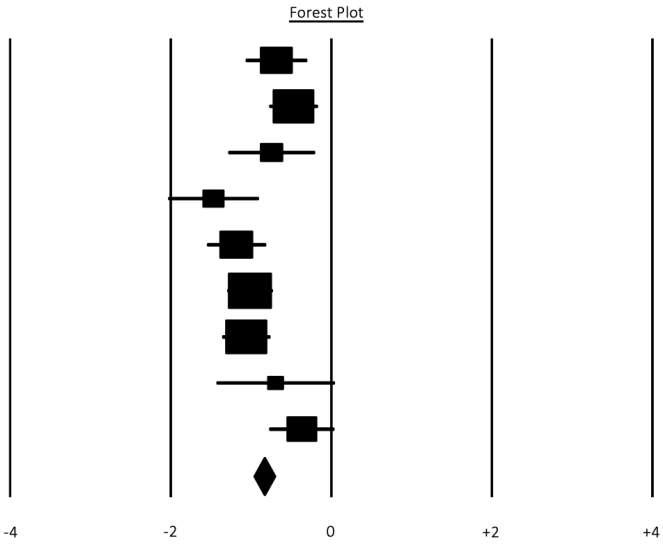

Figure 4. Forest plot depicting results for Performance IQ in children with HLHS relative to the normative mean. Hedges' *g* = estimate of effect size. Lower and Upper limits reflect the 95% confidence intervals for the Hedges' *g* statistic.

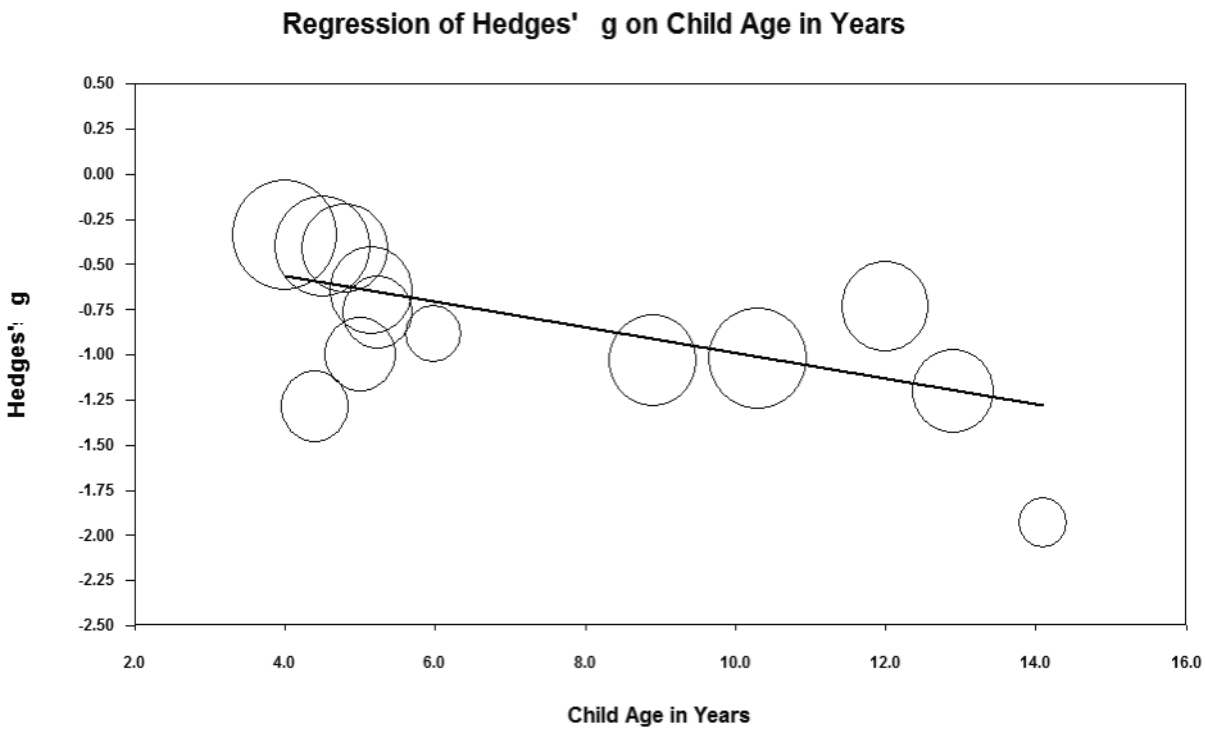

Figure 5. Scatter plot of meta-regression of Hedges' *g* for Full Scale IQ on child age. The x-axis reflects the mean child age in years for each study. The y-axis reflects the magnitude of the effect, indexed by Hedges' *g*.

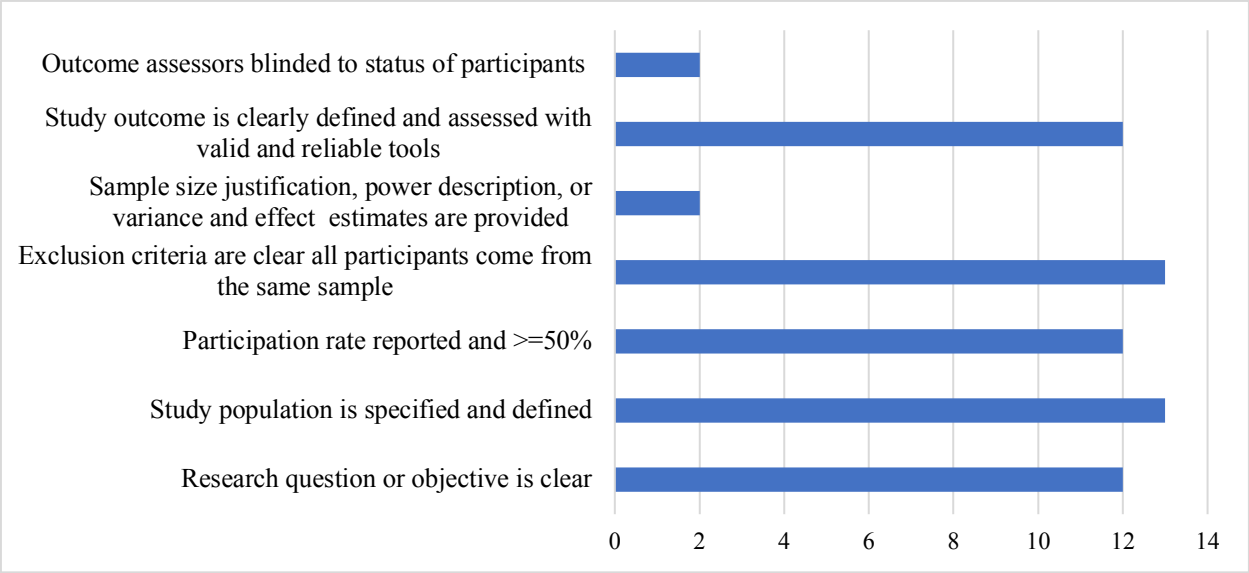

Figure 6. Study quality ratings. The X axis reflects the number of studies reporting each criterion from the National Institutes of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (NHLBI, 2014).

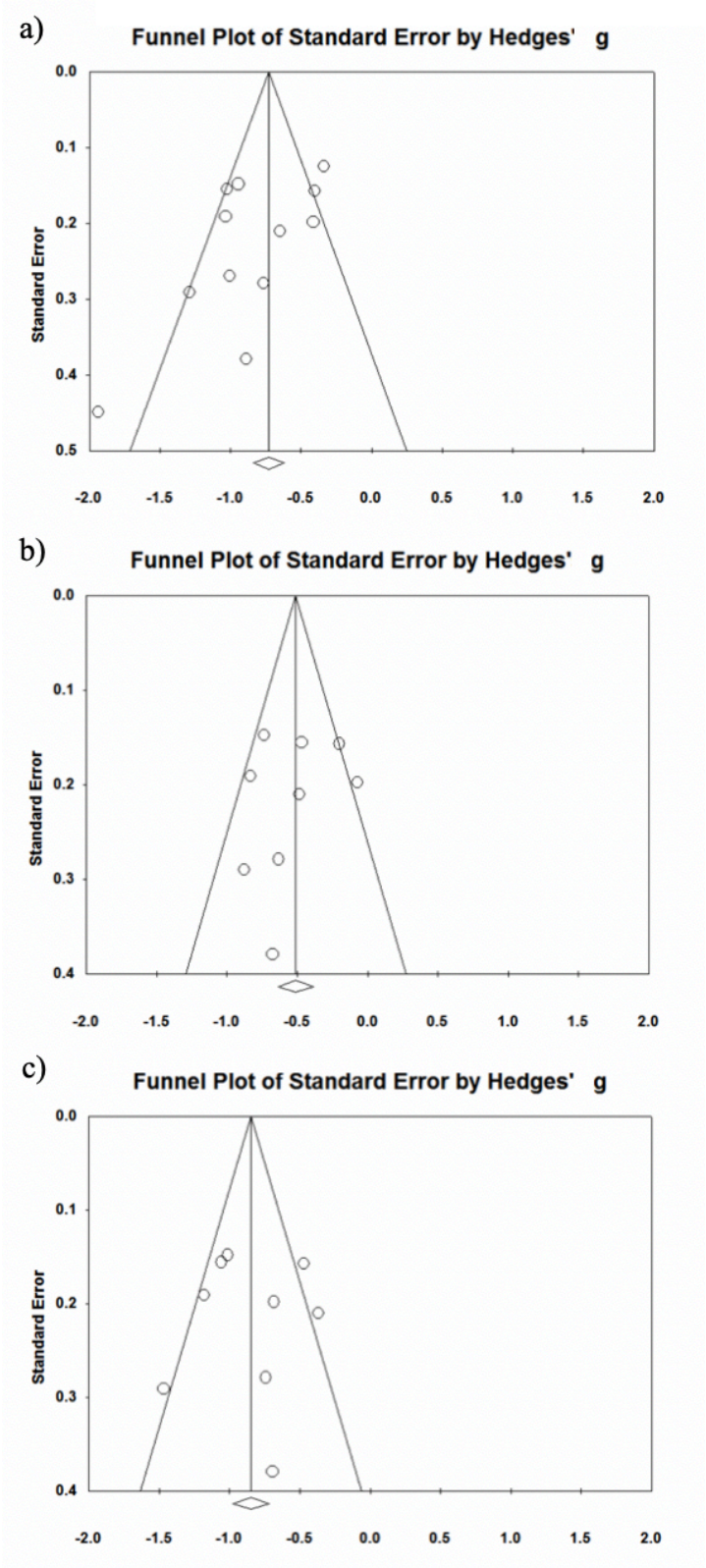

Figure 7. Funnel plots for the relation between the standard error and Fisher's *z* assessing publication bias. (a) Full Scale IQ; (b) Verbal IQ; (c) Performance IQ.